Stereospecific synthesis of N-tosyl derivatives of dihydroconduramine E-2 and *ent*-F-2

Izzet N. Kurbanoglu,[a]* Senol Besoluk[a] and Mustafa Zengin[b]

[a]*Department of Science Education, Faculty of Education, Sakarya University, 54300, Hendek/ Sakarya, Turkey*
[b]*Department of Chemistry, Faculty of Art and Sciences, Sakarya University, 54100, Esentepe/ Sakarya, Turkey*
E-mail: kurbanoglu@sakarya.edu.tr

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.a07

Abstract

Conduramines, dihydroconduramines and structurally related compounds belong to an important class of glycosidase inhibitors which are essential elements of many biologically active compounds. The synthesis and characterization of N-tosyl dihydroconduramine derivatives **9a** and **10a** starting from cyclohexadiene were carried out in the current study. The oxazolidinone **15** was prepared by the palladium-catalyzed reaction of bis-carbamate **14,** synthesized from cyclohexenediol, derived in two steps from cyclohexadiene. Hydrolysis of **15** was achieved with methanolic potassium carbonate to afford **18** and the ketalization gave **21** in good yield. Osmylation of the double bond and acid-mediated acetonide removal of **21** gave 4-methyl-*N*-((1*S*,2*R*,3*S*,6*S*)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide **9a**. The epoxidation of **21** followed by acid-mediated epoxide ring opening and subsequent acetonide removal produced 4-methyl-*N*-((1*S*,2R,3*R*,6*S*)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide **10a**. The molecules may be evaluated for biological activity.

Keywords: Aminocyclitols, conduramines, dihydroconduramines, glycosidase inhibitors

Introduction

Glycosidases are involved in a wide range of anabolic and catabolic processes such as intestinal digestion, lysosomal catabolism of glycoconjugates and post-translational processing of glycoproteins.[1-4] The possibility of modifying or blocking these processes using glycosidase-inhibiting sugar mimics for biological and therapeutic applications has attracted much attention,[5,6] especially in relation to cancer,[7,8] viral infection,[9,10] genetic disorders,[11-13] diabetes [14] and obesity.[15] The biomedical and biotechnological applications of glycosidase-inhibiting sugar mimics have been reviewed.[16] Inhibitors of glycoside-processing enzymes share structural homology with the natural

enzymatic substrates that are often aminohydroxy-substituted five or six-membered heterocyclic rings.[17,18]

Conduramines, dihydroconduramines and structurally related compounds belong to an important class of glycosidase inhibitors which are essential elements of many biologically active compounds.[19-27] In particular, conduramines **1-3** and dihydroconduramines **4-6** apart from their use as probes for biological functions of oligosaccharides have also served as important synthetic precursors of amino- and diaminocyclitols and many other biologically active compounds (Figure 1).[28-30]

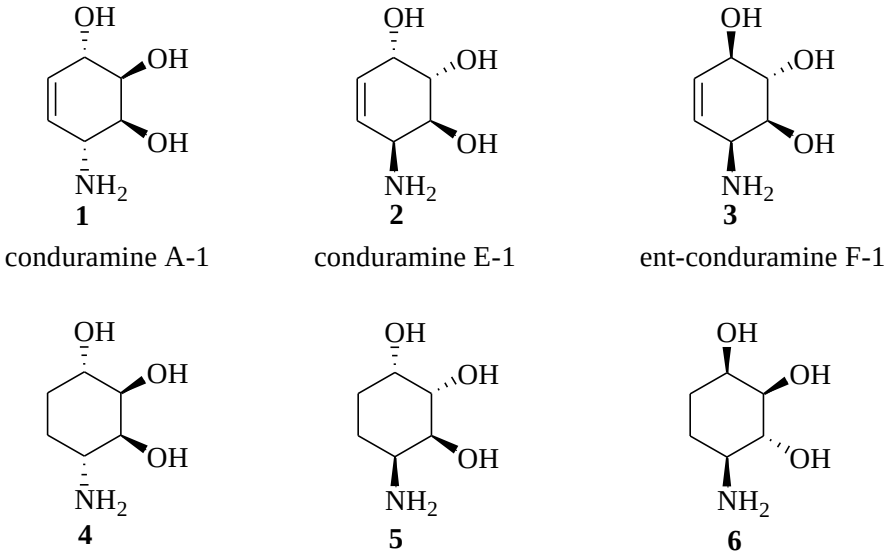
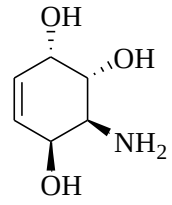


Figure 1

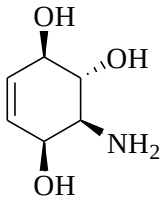
These features contribute to the importance of conduramines and have motivated the efforts made towards the development of new and efficient synthetic routes. Synthesis of conduramines **7** and **8**, their dihydroconduramines analogues **9** and **10**, and N-tosyl derivatives **9a** and **10a** have not yet been described (Figure 2).[31]

Consequently in the current study we report the synthesis and characterization of N-tosyl dihydroconduramine derivatives (±)**9a** and (±)**10a** starting from cyclohexadiene. The compounds **9a** and **10a** are likely to have similar biological activities with their analogues and may be used as intermediates for the synthesis of new biologically active substances.



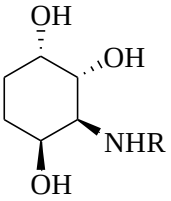
7

conduramine E-2



8

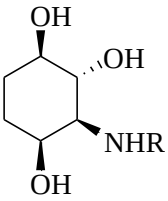
ent-conduramine F-2



dihydroconduramine E-2

9 R = H

(±) **9a** R = Ts



ent-dihydroconduramine F-2

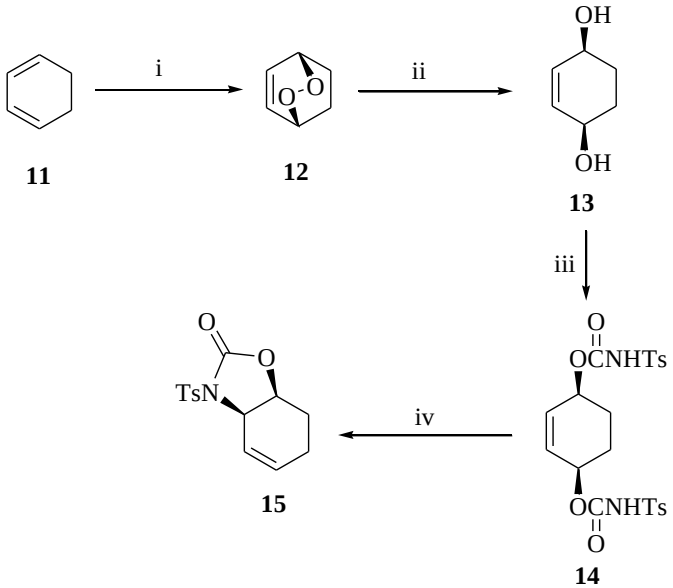
10 R = H

(±) **10a** R = Ts

Figure 2

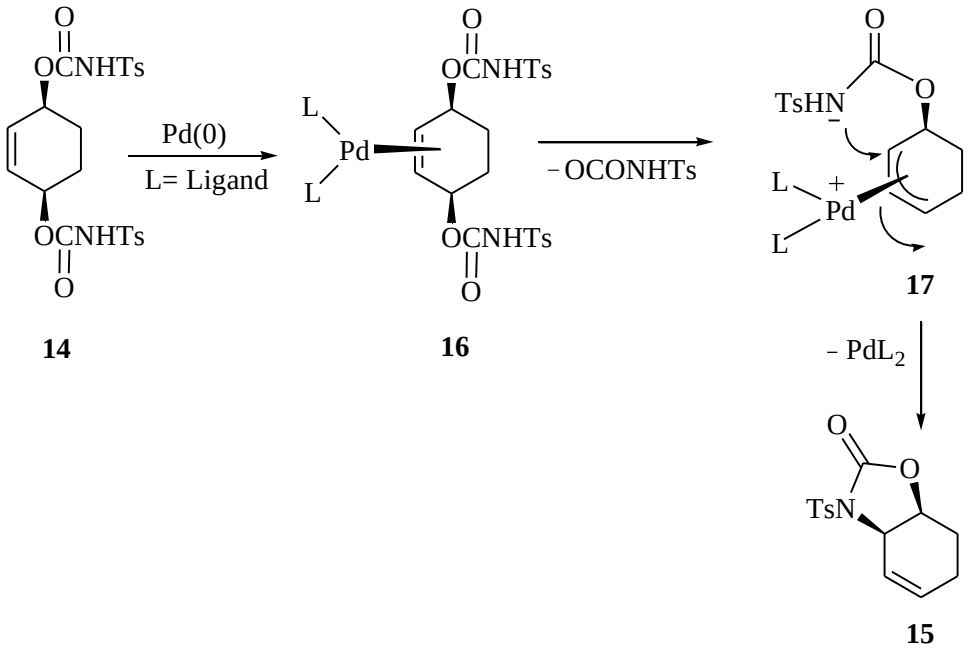
Results and Discussion

The oxazolidinone **15** was first prepared by the palladium-catalyzed reaction of bis-carbamate **14,** that was available from cyclohexadiene in three steps (Scheme 1).



Scheme 1. (i) $^1O_2$, TPP, hν, $CHCl_3$, rt, 10 h, 80%; (ii) Thiourea, MeOH, rt,; (iii) 2eq. Ts-N=C=O, THF, rt.; (iv) $(dba)_3Pd_2$ $CHCl_3$, P(O *i* Pr)$_3$, THF, (-5 to 25 ºC), 24 h, 40%.

The starting material cyclohexene endoperoxide **12** was synthesized from the photooxygenation reaction of 1,3-cyclohexadiene **11** as reported by Balci.[32] The endoperoxide **12** was performed with thiourea under mild conditions to give diol **13** in quantitative yield. In this reaction, since only the oxygen-oxygen bond in **12** was cleaved, the configurations of carbon atoms were preserved. The reaction of diol **13** with 2 equivalents of toluenesulfonyl isocyanate formed bis-carbamate **14**.[33] The palladium-catalyzed desymmetrization of bis-carbamate **14** was confirmed to give the monosubstitution product oxazolidin-2-one **15**. The mechanism of this desymmetrization reaction has been reported by Trost (Scheme 2).[34,35]



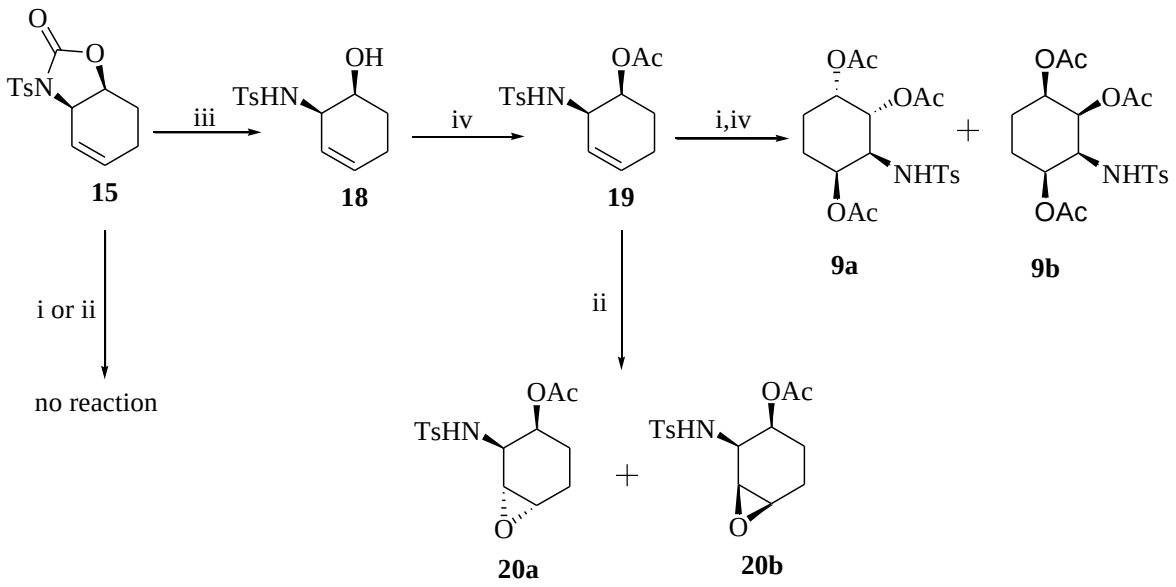
Scheme 2

The bis-carbamate **14** was treated with 2.5 mol% of palladium catalyst solution that was prepared with tris (dibenzylideneacetone)-dipalladium chloroform complex and 7.5 mol % of the ligand triisopropylphosphine.[36] The mixture was purified by chromatography on a silica gel column with CH_2Cl_2/hexane (30:70) as eluent to give oxazolidinone **15** in 40% yield. The structure of **15** was confirmed by ^1H and ^{13}C NMR spectroscopy.

Initially, for the synthesis of N-tosyl derivatives of dihydroconduramine E-2 and *ent*-F-2, direct epoxidation and cis-dihydroxylation of the double bound in **15** was attempted with *m*-CPBA and catalytic osmium tetraoxide at various temperatures and durations, however both reactions were unsuccessful.

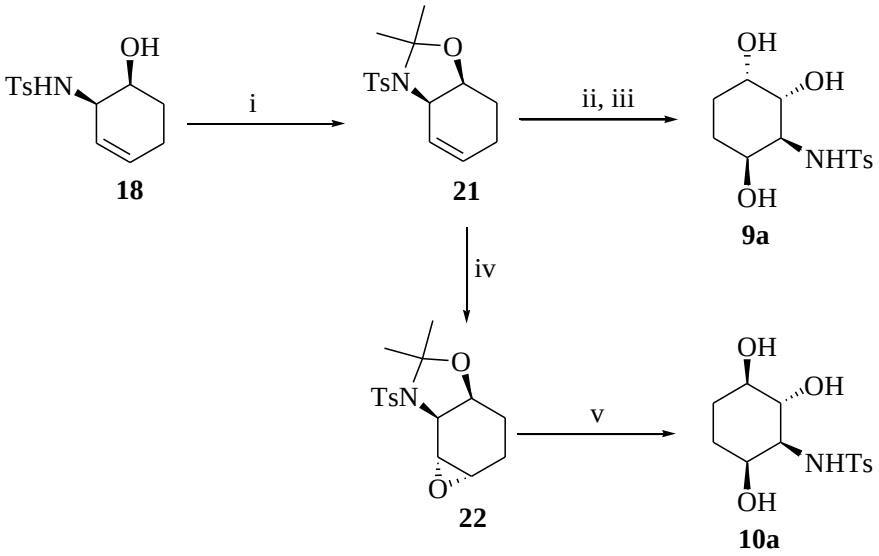
As a second strategy, cis-aminoalcohol **18** was prepared by the hydrolysis of **15** with methanolic potassium carbonate. The compound **18** was converted into acetate **19** by the treatment with AcCl in methylene chloride. The dihydroxylation of **19** was obtained as a mixture of **9a** and **9b** isomers, and the epoxidation of **19** also formed a mixture of **20a** and **20b** isomers. The results of ^1H and ^{13}C

NMR showed that **9a** was the main product of the first reaction and **20a** was the main product of the second reaction (Scheme 3).



Scheme 3. (i) OsO_4/NMO, THF-H_2O, 2:1, (0 ºC-rt), 48 h, 85%; (ii) *m*-CPBA, $CHCl_3$, Na_2HPO_4, 48 h, reflux, 95%; (iii) K_2CO_3, MeOH, rt., 18 h, 90%; (iv) AcCl, CH_2Cl_2, rt., 6 h, 100%.

Since the aim of this study was the stereospecific synthesis of N-tosylhydroconduramine derivatives **9a** and **10a**, we followed the third strategy for their synthesis (Scheme 4).



Scheme 4. (i) $Me_2C(OMe)_2$, *p*-TsOH, benzene, 4 h, reflux, 90%; (ii) OsO_4/NMO, THF-H_2O, 2:1, (0 ºC-rt), 48h, 70%; (iii) 10% AcOH-THF, 1:1, 2 h, refux, 90%; (iv) *m* – CPBA, $CHCl_3$, Na_2HPO_4, 60 h, refux, 90%; (v) 10% AcOH-THF, 1:1, 72 h, reflux, 90%.

In order to decrease the conformational flexibility of the cyclohexene skeleton and to influence the further stereoselective transformations, the ketalization of **18** was conducted. The bicyclic ring is cis-fused and the methyl groups of the oxazolidine **21** that point above the plane of the olefin may also force the electrophile to approach anti, thus reinforcing the anti directing effect of the allylic amino moiety.[37] Such a directing effect may also rationalize the stereochemical outcome of both the osmylation of **21** followed by acid-mediated acetonide removal, which provides (±)**9a** as a single isomer and the epoxidation of **21**, which provides **22** as a single isomer. In addition, the steric and conformational effects of the bicyclic ring system influenced stereoselectivity of the epoxide opening reaction. Thus, acid-mediated epoxide ring opening and subsequent acetonide removal of 22 obtained (±)**10a** as a single isomer. Compounds (±)**9a** and (±)**10a** were characterized by 2D spectroscopy, namely COSY, NOESY as well as by the ^{13}C NMR data. Careful examination of all these reaction mixtures did not reveal the formation of any other diastereoisomer.
In conclusion, we have described syntheses of N-tosyl derivatives of dihydroconduramine E-2 and ent-F-2 that can be used for various biological studies.

Acknowledgements

The authors greatly acknowledge the Scientific and Technical Research Council of Turkey (TUBITAK) for financial support (Project No: 106T374).

Experimental Section

General. Solvents were purified and dried by the standard procedures before use. Melting points were determined on Electrotermal BI-9100 capillary melting apparatus and uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 (75) MHz Varian spectrometer. Infrared spectra were obtained from Shimatzu Fourier Transform Infrared Spectrophotometer (IR Prestige-21, 200VCE). Column chromatography was performed on silica gel 60 (70-230 mesh). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F_{254} analytical aluminum plates.

(1R,4S)-2,3-Dioxa-bicyclo[2.2.2]oct-5-ene (12). The endoperoxide **12** was synthesized by the photooxygenation reaction of cyclohexadiene as reported by Balci.[32]
(1R, 4S)-Cyclohex-2-ene-1,4-diol (13). The cyclohexenediol **13** was synthesized by the reduction of the endoperoxide with thiourea under mild conditions in quantitative yield.[32]
Meso-2-ene-1,4-diol diester (14). Bis-carbamate **14** was prepared with ene-diol as described by Trost and his co-workers.[33]
(3aR,7aS)-3-Tosyl-3,3a,7,7a-tetrahydrobenzo[*d*]ox- azol-2(6H)-one (15). The oxazolidin-2-one **15** was prepared with bis-carbamate according to the procedure reported by Trost and Patterson.[34,35]
(3aR,7aS)-2,2-Dimethyl-3-tosyl-2,3,3a,6,7,7a-hexa- hydrobenzo[*d*]oxazole (21). A mixture of carbamate **15** (2 g, 6.83 mmol) and potassium carbonate (1.7 g, 12.3 mmol) in methanol/ water

(47:3 mL) was stirred at room temperature for 18 h, when TLC (silica gel, 80% ethyl acetate/hexane) indicated complete reaction. The reaction mixture was made acidic with glacial acetic acid, and the solvent was removed *in vacuo*. The mixture was loaded onto a short column of silica gel and eluted with 80% ethyl acetate/hexane + 1% acetic acid to afford, upon removal of solvent *in vacuo*, 1.8 g of the cis-aminoalcohol **18**, as a white solid, 90% (white solid from chloroform solution). The cis-aminoalcohol **18** (1.8 g, 6.82 mmol) was dissolved in dry benzene (60 mL), and dimethoxypropane (40 mL) and then *p*-TsOH (100 mg, 0.52 mmol) were added. The reaction mixture was heated under reflux for 4 h, cooled to room temperature, and washed with the saturated solution of Na_2CO_3. The organic layer was decanted and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvents were evaporated in vacuum. The crude product was purified by chromatography through silica gel (CH_2Cl_2-hexane 2:8), to afford the acetonide **21** (1.86 g, 90%) as a white solid (ether-hexane), mp.: 109-110 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (A part of AA BB system, d, 2H, *J* = 8.5 Hz, aromatic), 7.38 (B part of AA BB system, d, 2H, J_{AB} = 8.3 Hz, aromatic), 5.82-5.75 (dt, 1H, *J* = 10.2 Hz, *J* = 9.9 Hz), 5.63-5.57 (d, 1H, *J* = 10.2 Hz), 4.16 (s, 2H, O-CH and N-CH), 2.60 (s, 3H, -CH_3), 2.22-1.65 (m, 4H, 2x-CH_2), 1.62-1.56 (s, 6H, 2x-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.46, 139.12, 129.81 (2C), 129.28, 127.52 (2C), 125.55, 97.01, 72.11, 56.50, 30.15, 26.03, 24.58, 21.76, 18.94. IR (ART) 3020, 2929, 1598, 1494, 1375, 1330, 1236, 1213, 1143, 1095, 1031, 929, 881, 817, 790, 742, 682, 665 cm.$^{-1}$ Anal. calcd for $C_{16}H_{21}NO_3S$ (307.41): C, 62.51; H, 6.89; N, 4.56; S, 10.43; Found: C, 62.30; H, 7.06; N, 4.67; S, 10.56.

4-Methyl-N-((1S,2R,3S,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide (9a). The acetonide **21** (1.9 g, 6.13 mmol) was dissolved in acetone-H_2O (15:7.5 mL), and then NMO:H_2O (0.9 g, 6.72 mmol) and a 0.5 M solution of OsO_4 in acetone (6.2 mL, 0.3 mmol) were successively added. The reaction mixture was rapidly stirred 48 h at room temperature and was quenched with a 10% solution of Na_2SO_3. Following removal of solvent *in vacuo*, the mixture was chromatographed on a column of silica gel with 5% methanol/ethyl acetate, and the solvents were evaporated *in vacuo* to give the crude diol. The crude diol was dissolved in a 1:1 mixture of 10% AcOH (10 mL) and THF (10 mL) and then was heated under reflux for 2 h. Removal of the solvent gave the crude product, which was crystallized from MeOH-acetone (4:1) to give **9a** as a white solid (1.18g, 90%), mp.: 190-192 ºC. ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 (A part of AA BB system, d, 2H, *J* = 8.5 Hz, aromatic), 7.34 (B part of AA BB system, d, 2H, J_{AB} = 8.2 Hz, aromatic), 4.60 (s, 3H, -OH), 3.94-3.91 (q,1H, *J* = 4.9, *J* = 2.6 Hz), 3.67-3.63 (dd, 1H, *J* = 9.3 Hz, *J* = 4.9 Hz), 3.40-3.36 (m, 1H, -NH), 3.37-3.30 (dd, 1H, *J* = 3.2 Hz, *J* = 9.3 Hz), 3.29-3.14 (q, 1H, *J* = 4.6 Hz, *J* = 3.2 Hz), 2.4 (s, 3H, -CH_3), 1,77-1,69 (m, 2H), 1.59-1.46 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 143.41, 138.50, 129.46 (2C), 127.05 (2C), 69.86, 57.27, 48.72, 47.02, 25.87, 24.95, 20.35. IR (ART) 3485, 3300, 3290, 3219, 2990, 2927,1598, 1435, 1336, 1303, 1151, 1091, 1037, 1016, 956, 846, 815, 657 cm.$^{-1}$ Anal. calcd for $C_{13}H_{19}NO_5S$ (301.36): C, 51.81; H, 6.35; N, 4.65; S, 10.64; Found: C, 51.68; H, 6.47; N, 4.77; S, 11.04.

Epoxide (22). The oxazolidine **21** (2 g, 6.5 mmol) was dissolved in $CHCl_3$ (40 ml), *m*-CPBA (3.5 g, 13 mmol) and Na_2HPO_4 (2.5 g, 17.4 mmol) were added and the resulting white suspension was heated under reflux for 60 h. After addition of the saturated solution of $Na_2S_2O_3$, the aqueous layer

was extracted with CH_2Cl_2. The combined extracts were washed with the saturated solution of Na_2CO_3 and dried over $MgSO_4$. The solvent was evaporated in vacuum and the crude product was purified by chromatography through silica gel (CH_2Cl_2 -hexane 3:7), to afford the epoxide **22** (1.9 g, 90%) as a white solid (ether-hexane), mp.: 115-117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (A part of AA BB system, d, 2H, *J* = 8.2 Hz,), 7.30 (B part of AA BB system, d, 2H, J_{AB} = 7.9 Hz, aromatic), 3.90 (s, 2H), 3.23-3.19- (d,1H, *J* = 3.8 Hz), 3.19-3.18 (dd, 1H, *J* = 3.8, *J* = 14.0 Hz), 2.40 (s, 3H, -CH_3), 2.06-1.89 (dt, 2H, *J* = 14.0 Hz, *J* = 7.9 Hz), 1.69 (s, 3H, -CH_3), 1.65-1.60 (t, 2H, *J* = 7.9 Hz), 1.52 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.85, 137.94, 129.75 (2C), 127.66 (2C), 97.27, 70.12, 55.23, 52.53, 52.40, 30.37, 25.05, 21.69, 18.11, 17.76. IR (ART) 3010, 2937, 1597, 1430, 1371, 1334, 1244, 1143, 1103, 1093, 1031, 989, 871, 815, 790, 740, 659 cm.$^{-1}$ Anal. calcd for $C_{16}H_{21}NO_4S$ (323.41): C, 59.42; H, 6.54; N, 4.33; S, 9.91; Found: C, 58.79; H, 6.60; N, 4.23; S, 9.62.

4-Methyl-*N*-((1S,2R,3R,6S)-2,3,6-trihydroxycyclohexyl)benzenesulfonamide(10a). Magnetically stirred solution of epoxide **22** (2 g, 6.18 mmol) in a 1:1 mixture of 10% AcOH (15 mL) and THF (15 mL) was heated under reflux for 72 h. Removal of the solvent gave the crude product, which was crystallized from MeOH-ether (4:1) to give **10a** as a white solid (1.68 g, 90%), mp.: 224-226 ºC. ^{1}H NMR (300 MHz, DMSO) δ 7.80 (A part of AA BB system, d, 2H, *J* = 8.5 Hz, aromatic), 7.34 (B part of AA BB system, d, 2H, J_{AB} = 8.2 Hz, aromatic), 4.90 (s, 3H, -OH), 3.76-3.62 (dt, 1H, *J* = 11.4, *J* = 10.8 Hz), 3.36-3.42 (m, 1H, -NH), 3.31-3.30 (dt, 1H, *J* = 2.6 Hz, *J* = 9.0 Hz), 3.31-3.29 (dd, 1H, 2.9 Hz, *J* = 11.4 Hz), 2.94-2.93 (dd, 1H, *J* = 2.6 Hz, *J* = 2.9 Hz), 2.4 (s, 3H, -CH_3), 1.67-1.61 (m, 2H), 1.45-1.36 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 142.64, 139.87, 129.85 (2C), 127.34 (2C), 73.45, 72.96, 68.14, 61.14, 28.78, 27.20, 21.64. IR (ART) 3473, 3396, 3329, 3280, 3010, 2933,1600, 1433, 1375, 1298, 1269, 1145, 1128, 1091, 1051, 999, 945, 848, 808, 667 cm.$^{-1}$ Anal. calcd for $C_{13}H_{19}NO_5S$ (301.36): C, 51.81; H, 6.35; N, 4.65; S, 10.64; Found: C, 51.54; H, 6.20; N, 4.80; S, 11.46.

References

1. Borges de Melo, E.; da Silveira Gomes, A.; Carvalho, I. *Tetrahedron* **2006,** 62, 10277 10302.
2. Asano, N.; Nash, J. R.; Russell J. Molyneux, J. R.; George W. J. Fleet, J. W. G T*etrahedron: Asymmetry* **2000,** *11*, 1645.
3. Rye, C. S.; Withers, S. G. *Curr. Opin. Chem. Biol.* **2000**, *4*, 573.
4. Zechel DL, Withers SG: *Curr. Opin. Chem. Biol.* **2001**, *5*, 643.
5. Asano, N. *Glycobiology* **2003,** *13*, 93R-104R.
6. Asano, N. *J Enzym. Inhib. Med. Chem.* **2000**, 15, 215.
7. Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, 1, 935.
8. Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Lizuka, Y. *J. Med. Chem*. **1997**, 40, 2626.
9. Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, 181, 180.
10. Mehta, A.; Rudd, P. M.; Block, T. M.; Dwek, R. A. *Biochem. Soc. Trans.* **1997**, 25, 1188.

11. Fan, J.-Q. *Trends Pharmacol. Sci*. **2003**, 24, 355.
12. Futerman, A. H.; van Meer, G. *Nat. Rev. Mol. Cell Biol*. **2004**, 5, 554.
13. Pastores, G. M.; Barnett, N. L. *Expert Opin. Emerg. Drugs* **2005**, 10, 891.
14. Scheen, A. *J. Drugs* **2003**, 63, 933.
15. Moyers, S. B. *J. Am. Dietetic Assoc*. **2005**, 105, 948.
16. Winchester, B. G.; Fleet, G. W. J. *Glycobiology* **1992**, 2, 199.
17. Kajimoto, T.; Lui, K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A. Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, 113, 6187.
18. Sakuda, S.; Isogai, A.; Matsumoto, S.; Suziki, A. *Tetrahedron Lett.* **1986**, 27, 2475.
19. Lysek, R.; Favre, S.; Vogel, P. *Tetrahedron* **2007**, 63, 6558.
20. Lysek, R.; Schütz, C.; Favre, S.; O'Sullivan, C. A.; Pillonel, C.; Krülle, T.; Jung, M. J. P.; Clotet-Codina, I.; Este, A. J.; Vogel, P. *Bioorg. Med. Chem.* **2006,** 14, 6255.
21. Kelebekli, L.; Çelik, M.; Şahin, E.; Kara, Y.; Balci, M. *Tetrahedron Lett.* **2006**, 47, 7031.
22. Lysek, R.; Schütz, C.; Vogel, P. *Bioorg. Med.Chem. Lett.* **2005**, 15, 3071.
23. Lysek, R.; Schütz, C.; Vogel, P. *Helv. Chim. Acta* **2005,** 88, 2788.
24. Freeman, S.; Hudlicky, T. *Bioorg. Med. Chem. Lett.* **2004**, 14, 1209.
25. Elango, S.; Wang, Y. C.; Cheng C. L.; Yan, T. H. *Tetrahedron Lett.* **2002,** 43, 3757.
26. Leung-Toung, R.; Liu, Y.; Muchowski, J. M.; Wu, Y. *J. Org. Chem.* **1998**, 63, 3235.
27. Werbitzky, O.; Klier, K.; Felber, H. *Leibigs Ann. Chem.* **1990,** 3, 267.
28. Pandey, G.; Tiwari, N. K.; Puranik, G. V. *Org. Lett.* **2008**, 10, 3611.
29. Hudlicky, T.; Olivio, F. H. *Tetrahedron Lett.* **1991**, 32, 6077.
30. Hesegawa, A.; Nishimura, D.; Kurokawa, T.; Nakajima, M. *Agric. And Biol. Chem. (Japan)* **1972**, 36, 1773.
31. Lysek, R.; Vogel, P. *Tetrahedron* **2006**, 62, 2733.
32. Balci, M. *Chem. Rev.* **1981,** 81, 91.
33. Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992,** 114, 9327.
34. Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, 63, 1339.
35. Trost, B. M.; Dudash, J. Jr.; Hembre, E. J. *Chem. Eur. J.* **2001,** 1619.
36. Trost, B. M.; van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, 115, 444.
37. Angelaud, A.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, 64, 9613.